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HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
FOLEY, SHANON A	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 07/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/965,135	GUNZBURG ET AL.	
	Examiner	Art Unit	
	Shanon Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 8-22* is/are pending in the application.

4a) Of the above claim(s) *9-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 8, 18-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/925214.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

In the amendment submitted April 22, 2004, applicant amended claims 1, 5, 18, 21 and 22 and canceled claims 6 and 7. Claims 9-17 remain withdrawn from consideration due to non-elected subject matter. Claims 1-5, 8 and 18-22 are under consideration.

Election/Restrictions

This application contains claims 9-17, drawn to an invention nonelected with traverse in the reply filed on June 24, 2003. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-4 are rejected under 35 U.S.C. 102(a) as being anticipated by Lapeyre et al. (WO 95/00178).

Applicant asserts that Lapeyre et al. do not anticipate the invention as amended because Lapeyre et al. do not teach the addition of a therapeutic gene to the superantigen (Sag) encoding gene cassette.

Applicant's amendments to the claims as well as the arguments have been fully considered, but are found unpersuasive. Claim 1 now requires that "at least one sequence encoding a peptide selected from the group consisting of: a therapeutic peptide and a non-

therapeutic peptide" be present in the recombinant vector along with a sequence encoding a Sag-activity peptide (emphasis added).

Lapeyre et al. anticipate a recombinant vector comprising a nucleotide sequence capable of infecting and directing the expression of a coding sequence and a sequence encoding a peptide with Sag activity, see claims 1, 4-17 and 20.

Lapeyre et al. also anticipate a sequence encoding a non-therapeutic peptide, such as CAT, present in the vector along with the Sag gene cassette, see claims 2, 11-13 and page 12, lines 4-8. Therefore, Lapeyre et al. anticipate the instant claims regarding the expression of a non-therapeutic gene in addition to the Sag-activity peptide.

Lapeyre et al. also anticipate the expression of a therapeutic peptide in addition to Sag, see page 6, line 36 to page 7, line 4. Lapeyre et al. specifically teach that a preferred embodiment includes a DNA comprising "a toxin gene and preferably the gene encoding a cytolytic enterotoxin... such as *Staphylococcus aureus* enterotoxin A (SEA)". Claim 8 of Lapeyre et al. specifies that the Sag region of the DNA construct is *Staphylococcus aureus* enterotoxin A. Therefore, a toxin gene that is expressed in addition to the Sag cassette is an additional therapeutic gene. On page 8, line 32 to page 9, line 3, Lapeyre et al. discuss toxin cassettes and lists examples of the genes encoded by the cassette. In addition, Lapeyre et al. specifically contemplate the gene that encodes a toxin be under the control of a promoter, see page 9, lines 26-29. Therefore, Lapeyre et al. also anticipate the instant claims regarding the expression of a therapeutic gene, i.e. a toxin, in addition to the Sag-activity peptide.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 8 and 18-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gunzburg et al. (Nature. 1993; 364 (July 8): 154-158), Gilboa (US 5,658,775) and Miller et al. (US 5,219,740).

The claims are drawn to a recombinant replication-defective retroviral vector capable of promoter conversion comprising a 5' LTR comprising the structure U3-R-U5, a sequence encoding a peptide with Sag activity and a 3' LTR comprising a completely or partially deleted U3 region that is replaced by a promoter expressing heterologous DNA sequences followed by R-U5. The claims also require a host cell infected with the retroviral vector. The recombinant vector is used for amplification of B- or T-cells. The claims have been amended to require that the recombinant vector expresses sequences encoding a therapeutic peptide.

Gunzburg et al. identify a promoter located in the U3 region of the 5' MMTV LTR and splice donor/acceptor sites expressing an endogenous superantigen (Sag), see Figure 1a. Gunzburg et al. teach that superantigen expression results in T-cell proliferation, see the abstract and the last paragraph on page 158. Gunzburg et al. do not teach a replication-defective retrovirus comprising a completely or partially deleted U3 region that is replaced by a promoter expressing heterologous DNA sequences followed by R-U5 or a host cell comprising the retroviral construct.

Gilboa teaches a murine retroviral vector comprising a 5' LTR and a completely or partially deleted U3 region of the 3'LTR replaced by a heterologous promoter and a DNA sequence followed by R-U5, see claims 1, 4, 9, 10, 13, 15-17, 19-24 and Figures 4 and 10. Gilboa also teach a host cell complementing elements that are missing in the recombinant vector deficient in viral replication, see column 2, lines 18-30. With respect to the new limitation of a therapeutic protein that is now required in the retroviral vector, Gilboa teach self-inactivating vectors (SIN), which expresses a gene between the 5' LTR and the 3' LTR, see column 4, line 56 to column 5, line 26, Figure 2C and claim 25. Gilboa also teach a retroviral vector expressing a non-therapeutic gene, such as a selectable marker or a therapeutic protein, such as human adenosine deaminase (ADA), a sequence from a pathogen or a hemoglobin protein, see column 8, line 66 to column 9, lines 1 and 13-29.

One of ordinary skill in the art at the time the invention was made would have been motivated to replace at least a portion of the 3' LTR U3 region with a heterologous promoter and DNA sequence, taught by Gilboa, into the MMTV of Gunzburg et al. to generate self-inactivating vectors and introduce therapeutic genes to a host, see the previous citations of Gilboa. The proviral DNA from the vectors of Gilboa are transcriptionally inactive, which results in the expression of the heterologous insert. One of ordinary skill in the art would also have been motivated to delete at least a portion of the 3' LTR U3 region within the MMTV of Gunzburg et al. to disable activation of cellular oncogenes, see column 5, lines 5-14 of Gilboa. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of producing an MMTV expressing Sag and 3' LTR U3 region comprising a heterologous promoter

and DNA sequence because Gunzburg et al. specifically identify the nucleotides and splice sites required for Sag expression and Gilboa teach that self-inactivating vectors are generated by deleting or replacing any portion of the 3' LTR U3 region. Therefore, the segments required for expression of Sag, taught by Gunzburg et al., and the mutations within the 3' LTR U3 region, taught by Gilboa do not overlap.

Applicant asserts that an obviousness rejection requires that the prior art would have suggested to one of ordinary skill in the art the claimed process. Applicant further asserts that a reasonable expectation of success should not be found in applicant's disclosure, but in the prior art.

Applicant's assertions are in agreement with the instant case of prima facie obviousness in view of the combined teachings of Gilboa and Gunzburg et al. The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation is found in the references themselves. One of ordinary skill in the art at the time the invention was made would have been motivated to generate self-inactivating vectors, disable activation of cellular oncogenes and introduce therapeutic genes to a host, taught by Gilboa (see column 2, lines 18-30, column 4, line 56, column 5, lines 5-14 and 26, Figure 2C, column 8, line 66 to column 9, lines 1 and 13-29 and claim 25) with the T-cell proliferating MMTV

retrovirus of Gunzburg et al., see Figure 1a, the abstract and the last paragraph on page 158.

The teachings of Gunzburg et al. and Gilboa also provide a reasonable expectation of success for combining the teachings. Gunzburg et al. identify a promoter located in the U3 region of the 5' MMTV LTR and splice donor/acceptor sites expressing an endogenous superantigen (Sag) that results in T-cell proliferation, see Figure 1a, the abstract and the last paragraph on page 158. Gilboa teaches a replication-defective (SIN), therapeutic retroviral construct possessing an intact 5' LTR of any retrovirus, which encompasses retrovirus MMTV, see the previous citations as well as claims 1, 16-18 and 23-25. Therefore, the ordinary artisan would have a reasonable expectation for combining the MMTV of Gunzburg et al. with the mutations within the 3' LTR U3 region, taught by Gilboa, because the segments required for expression of Sag and the manipulations of the retrovirus construct required by Gilboa do not overlap.

Applicant argues that neither Gunzburg et al. nor Gilboa teach a recombinant vector comprising Sag gene and a therapeutic gene. Applicant further argues that neither Gunzburg et al. nor Gilboa teach a recombinant retroviral vector that is capable of promoter conversion and is replication defective, and comprises a completely or partially deleted U3 region that is replaced by a promoter that directs the expression of a DNA sequence.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Gunzburg et al. teach a retrovirus, MMTV, comprising Sag, see Figure 1a, the abstract and the last paragraph on page 158. Gilboa teach retrovirus constructs expressing therapeutic genes, see column 4, line 56 to column 5, line 26, Figure 2C, column 8, line 66 to column 9, lines 1 and 13-29 and claims 16-18 and 25. It is maintained that one of ordinary skill in the art at the time the invention was made would have been motivated to generate self-inactivating vectors, disable activation of cellular oncogenes and introduce therapeutic genes to a host, taught by Gilboa, with the T-cell proliferating MMTV retrovirus of Gunzburg et al.

Contrary to applicant's assertions, the combination of references teach a recombinant retroviral vector that is capable of promoter conversion and is replication defective, and comprises a completely or partially deleted U3 region that is replaced by a promoter that directs the expression of a DNA sequence. Although Gilboa does not mention "promoter conversion", page 6 of the instant disclosure lists the structural features of a vector capable of promoter conversion. These characteristics include an intact 5' LTR and a completely or partially deleted 3' U3 LTR that is replaced by a promoter that directs the expression of a DNA sequence. The retrovirus construct of Gilboa comprises an intact 5' LTR and a deleted 3' U3 region that is replaced by a promoter that directs the expression of a DNA sequence, see Figures 4, 7 and claims 1 and 8 for example. Since the retrovirus construct of Gilboa possess the same features required for a vector that is described as capable of promoter conversion, it is determined that the construct of Gilboa is capable of promoter conversion. As discussed previously, the retrovirus construct of Gilboa is also replication defective (SIN) because Gilboa teaches replacing "vital genes" with a gene of interest, see column 2, lines 18-45, Figures

2A, 2C, 5B, 7A, 9 and claim 25. Therefore, contrary to applicant's assertions, the retroviral construct of Gilboa comprises genes of interest within the body of the retroviral vector.

Applicant emphasizes the limitations of claim 5, which are:

a) a 5' LTR comprising the structure U3-R-U5 followed by

b) a sequence encoding a peptide with Sag activity followed by

c) a 3' LTR comprising a completely or partially deleted U3 region that comprises a heterologous DNA that includes elements that regulate expression of the coding sequence.

Applicant concludes from this discussion of these limitations that the instant retroviral vector has a promoter in the 5'LTR and the coding sequence is in the body of the vector.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that the heterologous insert is in the body of the retrovirus) is not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). While the structural components recited in claim 5 are required to be in operable linkage, the components are not required to be present in a specific order. There is also no limitation reciting that the heterologous insert is in the body of the retrovirus. The structural components that must be present are: a 5' LTR comprising U3-R-U5 and a 3' LTR comprising a completely or partially deleted U3 region that is replaced by a promoter that regulates the expression of heterologous DNA

fragments. Gilboa claims these structural components in claims 1 and 8. The instant construct also comprises a therapeutic peptide, but there is no limitation requiring that the peptide must be expressed within the body of the retrovirus or within the 3' U3 LTR. In either case, the construct of Gilboa comprises either or both, see the previous citations and claims 1 and 8 as well as claim 25 for example. The instant claims also require a peptide with Sag activity. Gilboa does not teach this limitation, but the MMTV of Gunzburg et al. possesses this structural limitation, see the abstract and the last paragraph on page 158. It is maintained that one of ordinary skill in the art at the time the invention was made would have been motivated to generate self-inactivating vectors, disable activation of cellular oncogenes and introduce therapeutic genes to a host, taught by Gilboa, with the T-cell proliferating MMTV retrovirus of Gunzburg et al. Further, the ordinary artisan would have a reasonable expectation for combining the MMTV of Gunzburg et al. with the mutations within the 3' LTR U3 region, taught by Gilboa, because the segments required for expression of Sag and the manipulations of the retrovirus construct required by Gilboa do not overlap.

In conclusion, the prior art specifically suggests the instant combination with a reasonable expectation of success for producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (571) 272-0898. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Shanon Foley
Patent Examiner, 1648